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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,191	10/15/2001	Audrey Goddard	GNE.2630P1C4	4728

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,191	GODDARD ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005 and 01 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-63,69 and 70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-63,69 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 23, 2005 has been entered.

Claims

2. Claims 58-63, 69 and 70 are pending in the instant application. Claims 58-63 have been amended as requested by Applicant in the Amendment filed May 23, 2005.

Withdrawn Objections and Rejections

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Priority Determination

4. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 120 or § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention.

Applicants' response has clarified that nucleic acid of SEQ ID NO: 505 and encoded protein of SEQ ID NO: 506 (PRO213-3) are the same as the sequences identified as PRO1330 (clone DNA30943) in provisional 60/100,038, which demonstrates a specific and substantial

utility for the nucleic acid, as a cancer diagnostic. Pages 61-69 of 60/100,038 demonstrate that this nucleic acid is amplified in a large number of lung tumors, which was corrected for aneuploidy. However, the effective priority date of the instant application is considered to be the filing date of this application, October 15, 2001, because the claimed invention is not supported by either a specific and substantial utility or a well established utility for the claimed polypeptides.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 58-62, 69 and 70 are indefinite because claims they recite a "native sequence" polypeptide having at least 80%, 85%, 90%, 95% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 506. The specification teaches on pages 121-122 that:

"A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide specifically encompasses naturally-occurring or truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms and naturally-occurring allelic variants of the polypeptide."

However, it is not clear how one of ordinary skill in the art would be able to determine if a sequence is "a native sequence" or not by looking at it.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 and 112, first paragraphs read as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 58-63, 69 and 70 remain rejected under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office actions, mailed June 2, 2004, at pages 5-9, March 16, 2005 at pages 3-10, and below.

Claims 58-63, 69 and 70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants' arguments (pages 7-24, Paper filed May 23, 2005) have been fully considered but are not fond to be persuasive for the following reasons. Applicant reviews the legal standard for patentable utility, with which the examiner takes no issue.

Applicant argues that the gene amplification assay is well-described in Table 9, showing that nucleic acids encoding PRO213-1 were significantly overexpressed in certain cancers such as colon, lung breast and other tumors as compared to the normal control, providing a patentable utility for the nucleic acids encoding PRO213-1 and their variants. This has been fully considered but is not found to be persuasive. While the data in Table 9 may provide a basis for

utility and enablement of PRO213-1 nucleic acid, it does not provide a basis for utility or enablement of the claimed polypeptides. The art supports this position by establishing that there is no strong correlation between gene amplification and increased mRNA or protein levels. See Pennica et al., and Gygi et al. of record. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy before the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay does not provide a comparison between the lung tumor samples and normal lung epithelium, or between colon tumor samples and normal colon tissue, and thus it is not clear that PRO213-1 is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. One skilled in the art would not conclude that PRO213-1 is a diagnostic probe for lung or colon cancer unless it is clear that PRO213-1 is amplified to a clearly greater extent in true lung or colon tumor tissue relative to non-cancerous lung or colon epithelium. Also, while it might be argued in hindsight that PRO213-1 would still be a marker at least for precancerous, or damaged, lung or colon epithelium, such is not suggested by the specification as originally filed and is not well-established in the *prior* art. Furthermore, even if it could be established that gene amplification is reflected by increased polypeptide levels, the claims are broadly drawn to polypeptides that can be variants of the polypeptide of SEQ ID NO: 506, including fragments and substitution variants. One skilled in the art would expect that such variant sequences would not reasonably be expected to show changed levels for a particular disease state.

Applicants submit the Declaration by Dr. Audrey Goddard, in which she states that a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer. Applicants assert that as the TaqMan realtime PCR method has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification, one of ordinary skill in the art would find it credible that PRO213-1 is a diagnostic marker of human lung cancer.

The Goddard Declaration filed under 37 CFR 1.132, filed Oct. 4, 2004 is insufficient to overcome the rejection of claims 58-63, 69 and 70 as set forth in the last Office action because: while the declaration and supporting references are convincing that the TaqMan realtime PCR method is very sensitive and can identify amplified genes, the claims are drawn to protein encoded by the PRO213-1 gene, and as discussed in the previous office actions and below, it is not predictable that gene amplification results in increased mRNA expression, or that increased mRNA expression results in increased protein production.

As a preliminary matter, Applicants submit that it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels, that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration, and accordingly, the question is not whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation.

The Examiner agrees that a strong or necessary correlation is not necessary to establish that gene amplification results in increased mRNA levels, and that increased mRNA levels results in increased protein levels, however the cited references discussed previously, as well as new references cited herein, do not demonstrate that is it more likely than not that gene amplification results in greater mRNA and protein levels.

Applicant argues that the Gygi et al. publication does not support the rejection. Applicant characterizes Gygi et al. as teaching that there is a general trend of increased protein levels from increased mRNA levels, and that at both low message levels and high message levels, the correlation coefficient was positive (10 copies/cell, 0.356 and abundant message, 0.94, respectively). Applicants also assert that Gygi et al. was studying steady-state yeast cells and not cancerous human cells, and that Gygi et al. admitted that "the present study has several potential sources of error related to the methods used to determine mRNA and protein expression levels." Applicants also point out that the authors admit that for the SAGE method, since more than 65% of the mRNA levels included in this study were calculated to 10 copies/cell or less, the error associated with these values may be quite large.

This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing an increase in DNA copy number in tumor samples for PRO213-1. There is no evidence regarding whether or not the PRO213-1 mRNA or polypeptide levels are also increased in these tumor samples. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Gygi et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon.

While Gygi et al. demonstrates that high levels of mRNA generally correlate with high levels of protein and that it appears that there is a general positive correlation between mRNA levels and protein levels, it has not been demonstrated that the PRO213-1 mRNA is over-expressed. Given the evidence provided by Gygi et al. and Pennica et al., it is clear that one skilled in the art would not assume that a increase in gene copy number would correlate with increased mRNA or polypeptide levels. Regarding the relevance of yeast genes, Applicant is directed to Lian et al. (2001, Blood 98:513-524) who show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

A very relevant reference, looking at transcript and encoded protein levels in human cancer cells, is Chen et al., Molecular and Cellular Proteomics, Vol. 1, pages 304-313, April 2002, who determined that in human carcinomas, for the majority of mRNAs and proteins, there is no correlation between transcript and protein levels. Chen et al. analyzed the abundance of 165 protein spots on two-dimensional gels corresponding to 98 individual genes in 76 lung adenocarcinomas and nine non-neoplastic lung tissues, and analyzed the abundance of the encoding mRNAs by microarrays. Among all 165 proteins the correlation coefficient values ranged from -.0467 to 0.442, and the mRNA/protein correlation coefficient also varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance (abstract). Although 21/98 genes showed a statistically

significant correlation between mRNA and protein, the majority of the proteins did not correlate with mRNA levels (page 311, first column). The authors suggest that in the first group, expression is likely to be regulated at the transcriptional level, while in the second group, expression is regulated by other mechanisms. In addition to the analyses of the correlation of mRNA/protein within the same tumor samples, the authors also tested the global relationship between mRNA and the corresponding protein abundance across all 165 protein spots using all 85 lung tissue samples, and observed a very wide range of normalized average protein and mRNA levels. The correlation coefficient generated was -0.025, and even for the 28 protein spots that showed a statistically significant correlation between individual mRNA and proteins, the correlation value was only –0.035 (see abstract and pages 311-312). The authors suggest that it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples, and teach that this conclusion is also supported by previous results from Anderson et al. (discussed below) and by Gygi et al. (discussed above), and in which both studies found a lack of correlation between mRNA and protein expression when average or overall levels were used (page 312, left column).

Anderson et al., Electrophoresis, Vol. 18, pages 533-537, 1997, found that there was a poor correlation (0.48) between mRNA and protein levels in liver cells (abstract, page 535). They suggest that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal importance in determining the net output of proteins (page 536, left column). Anderson et al. also reanalyzed the set of data for plasma proteins secreted by the liver that was published by Kawamoto et al., (Gene, 1996, Vol. 16, pages 1977-1981), in which the

mRNA-to-protein relationship for nine plasma proteins was 0.96. However, when albumin (which is well-separated from the cluster of the remaining eight and thus exercises a disproportionate influence on the correlation coefficient) was omitted from the calculation, the correlation coefficient is reduced to –0.19, which suggests a very poor correlation (page 536, right column).

The evidence as a whole clearly indicates that one skilled in the art would not assume that an increase in gene copy number would correspond with an increase in mRNA levels or protein levels without doing the empirical experimentation necessary to measure mRNA and protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the claimed polypeptides is not substantial; it is not in currently available form.

Applicant discusses the Orntoft, Hyman and Pollack references. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the amplification of PRO213-1

would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification.

Applicant refers again to the Polakis declaration, and argues that the examiner's criticism of the declaration for failing to provide data is improper. However, given the evidence in the art that increased DNA amplification does not necessarily correlate with increased mRNA levels, and that increased mRNA levels do not necessarily correlate with increased protein levels, the examiner maintains that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO213-1 are specifically amplified in tumors. Further research would have to be done in order to determine if PRO213-1 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to indicate PRO213-1 protein as a cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public.

Applicant argues that the examiner must accept an opinion from a qualified expert. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the nature of the fact is whether or not there is a correlation between mRNA levels and protein levels. There

is strong opposing evidence that there is no strong correlation between the two. The expert has a strong interest in the outcome of the case, as Dr. Polakis is employed by the assignee. Finally, while Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

Applicant criticizes the examiner's reliance on Hu et al. Applicant argues that Hu et al. is not relevant, as it does not discuss gene amplification. Applicant criticizes Hu et al. as being base don a statistical analysis of information published in the literature. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO213-1 mRNA levels are expressed at 10-fold or higher

levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO213-1 protein can be used as a cancer diagnostic. Furthermore, Applicant's attention is directed to Hanna et al. (of record, Pathology Associates Medical Laboratories, 1999), who show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Applicant criticizes Hu et al. as using faulty statistical analysis. This has been fully considered but is not found to be persuasive. Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc.

Applicant submits that similar to the HER-2/neu gene disclosed in Hanna et al., the PRO213-1 gene is a tumor associated gene, since the PRO213-1 gene is amplified in at least 35 primary lung and colon tumors and lung and colon cell lines, and that one of skill in the art would reasonably expect that the polypeptide is concomitantly overexpressed. However, as discussed in the previous office actions and supra, the preponderance of the art does not support that is it more likely than not that gene amplification results in greater mRNA and protein levels.

Applicant points to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on 04 October 2004, as establishing that, even is the protein were not over-expressed, the simultaneous testing of gene amplification and gene product over-expression would enable more accurate tumor classification. However, while this may be true, the specification does not

disclose such further testing of gene product over-expression. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public.

Applicant concludes that the present rejection is based on the application of an incorrect, elevated legal standard, on misconstruction of the references and erroneous conclusions drawn therefrom, and that the issue of patentable utility should be assessed on the totality of evidence, using the preponderance evidentiary standard. It is submitted that on the totality of evidence Applicants clearly established that the claimed invention has a substantial, specific and credible utility. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

This has been fully considered but is not found to be persuasive. However, this asserted utility is not substantial, since the specification does not provide a clear nexus between PRO213-1 and cancer occurrence or progression, for reasons noted above. Furthermore, the evidence of record clearly indicates that an increase in gene amplification does not correlate well with protein over-expression, for reasons noted above in the discussions of the individual references. Thus, the preponderance of the art supports the *prima facie* finding that an amplification of DNA would not form the basis for a substantial assertion of an association between PRO213-1 protein and cancer.

7. Claims 58-62, 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is set forth at pp. 9-10 of the Office Action mailed 02 February 2004 and pages 11-13 of the Office Action mailed 16 March 2005. Furthermore, the claims are directed to isolated "native sequence" polypeptides having at least 80%-99% identity to SEQ ID NO: 506, wherein the nucleic acid encoding the polypeptide is amplified in lung tumors. The specification discloses a single amino acid sequence for PRO213-1, SEQ ID NO: 506. There is a utility and enablement issue regarding whether or not the nucleic acid encoding PRO213-1 is amplified in lung tumors (see rejections under 35 U.S.C. §§ 101 and 112, first paragraph, above). Furthermore, the specification does not disclosure any variants of SEQ ID NO: 506, naturally occurring or not, nor whether such sequences are amplified in lung tumors.

Applicant's arguments (pp. 17-19, remarks submitted 03 June 2005) have been fully considered but are not found to be persuasive for the following reasons.

Applicant discusses the legal test for written description, with which the examiner takes no issue.

Applicant argues that the specification provides reduction to practice of a full-length PRO213-1 polypeptide of SEQ ID NO: 506, with or without its signal sequence. Applicant urges that such provides basis for the claimed genus of native polypeptide sequences with at least 80-99% sequence identity to SEQ ID NO: 506 which are functionally defined as being encoded by a nucleic acid that is amplified in lung or colon tumors. Applicant points to the specification's disclosure of methods for the determination of percent identity, and assays for

identification of nucleic acids and for the functional limitation in the claims. Applicant urges that the skilled artisan can readily test native polypeptide sequences for identity and whether or not the encoding nucleic acids are amplified in lung or colon tumors. This has been fully considered but is not found to be persuasive. The courts have specifically stated that if the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide, until the structure is disclosed, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case, SEQ ID NO; 506 has been disclosed, but no native sequence variants thereof have been disclosed regardless of whether or not they are encoded by nucleic acids that are amplified in tumors. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claim are a partial structure in the form of a recitation of percent identity, and a requirement that the encoding nucleic acids are amplified in lung or colon tumors. There is

not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Rejections over Prior Art

Claim Rejections - 35 USC § 102 and § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8.1 Claims 58-63 and 69 remain rejected under 35 U.S.C. 102(e) as being anticipated by Holtzman et al., U.S. Published Patent Application 20020028508, effective priority date April 23, 1998 (09/065,363), for reasons of record in the office action, mailed June 2, 2004, at pages 13 and 14.

8.2 Claim 70 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Holtzman et al., U.S. Published Patent Application 20020028508, effective priority date April 23, 1998 (09/065,363), in view of Hopp et al., U.S. Patent Number 5,011,912, April 1991, for reasons of record in the office action, mailed June 2, 2004, at pages 16-17.

Applicants traverse the rejections and submit that in order to overcome the 35 U.S.C. 102(e) and 103(a) rejections and support the priority claim, the Declaration by Goddard, Godowski, Gurney and Wood simply need to provide a disclosure commensurate in scope with the disclosure in both Holtzman et al. and Sheppard et al., and cite *In re Stempel* and *In re Moore*. The rejection over Sheppard et al. has been withdrawn because there is no longer a pending application claiming the invention.

The declaration of Goddard, Godowski, Gurney and Wood filed on October 4, 2004 under 37 CFR 1.131 has been considered but is ineffective to overcome the Holtzman et al. reference. The Holtzman et al. reference is a U.S. patent application publication of an abandoned application, which has a continuation 20050019810 that claims the rejected invention. MPEP § 2306 states that an affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention. If the references and this application are not commonly owned, the references can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the references and this application are commonly owned, the reference may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP § 718. Additionally, the declaration of Goddard, Godowski, Gurney and Wood declaration filed on October 4, 2004 is unsigned.

It is believed that all pertinent arguments have been answered.

Conclusion

9. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

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